Drug-induced modulation of gp130 signalling prevents articular cartilage degeneration and promotes repair.

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Public Summary:
OBJECTIVE: Human adult articular cartilage (AC) has little capacity for repair, and joint surface injuries often result in osteoarthritis (OA), characterised by loss of matrix, hypertrophy and chondrocyte apoptosis. Inflammation mediated by interleukin (IL)-6 family cytokines has been identified as a critical driver of proarthritic changes in mouse and human joints, resulting in a feed-forward process driving expression of matrix degrading enzymes and IL-6 itself. Here we show that signalling through glycoprotein 130 (gp130), the common receptor for IL-6 family cytokines, can have both context-specific and cytokine-specific effects on articular chondrocytes and that a small molecule gp130 modulator can bias signalling towards anti-inflammatory and antidegenerative outputs. METHODS: High throughput screening of 170 000 compounds identified a small molecule gp130 modulator termed regulator of cartilage growth and differentiation (RCGD 423) that promotes atypical homodimeric signalling in the absence of cytokine ligands, driving transient increases in MYC and pSTAT3 while suppressing oncostatin M- and IL-6-mediated activation of ERK and NF-kappaB via direct competition for gp130 occupancy. RESULTS: This small molecule increased proliferation while reducing apoptosis and hypertrophic responses in adult chondrocytes in vitro. In a rat partial meniscectomy model, RCGD 423 greatly reduced chondrocyte hypertrophy, loss and degeneration while increasing chondrocyte proliferation beyond that observed in response to injury. Moreover, RCGD 423 improved cartilage healing in a rat full-thickness osteochondral defect model, increasing proliferation of mesenchymal cells in the defect and also inhibiting breakdown of cartilage matrix in de novo generated cartilage. CONCLUSION: These results identify a novel strategy for AC remediation via small molecule-mediated modulation of gp130 signalling.

Scientific Abstract:
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